REMARKS

Claims 1-17 and 19-31 are pending. Claims 1-14, 17 (non-elected species), 20-25, and 27-30 have been withdrawn from consideration as being drawn to a non-elected invention. Claim 18 was previously cancelled. Claim 17 is cancelled herein without prejudice. New claims 32-34 are presented herein. Accordingly, claims 15-16, 19, 26, and 31, as amended, and new claims 32-34 are under consideration.

Claims 15-16, 19, 26, and 31 have been amended to better define the claimed subject matter. Support for these amendments is found in the original claims and throughout the specification. Specifically, support for amendment to claim 15 is presented in Figure 3 and description thereof at page 7, third paragraph; and in Example 1, at pages 17-21, wherein an envelope expression vector (pRVL; see also Figure 7) comprising a library of FeLV-A Env variants is described and with which an exemplary virus (EF) having an altered host range is generated; and in Example 2, at pages 21-22, wherein retroviruses expressing FeLV-A Env variants on their surface are described as exemplary retroviruses for the practice of the present invention; at page 8, first and third paragraphs, for example, wherein a retroviral expression vector expressing Env proteins containing random amino acid sequences are described and wherein support for the term FeLV Env variant is presented; at page at page 17, third paragraph, wherein Variable Region A (VRA) is described as an exemplary receptor-determining region of feline leukemia viruses; in Figure 6 and description thereof at page 8, third paragraph, wherein a sequence comparison of the VRA receptor-determining domain of feline leukemia virus subgroup A and subgroup C is shown and amino acid substitutions are illustrated; at page 20, first paragraph, wherein infecting various host populations is described; and at page 23, third paragraph, wherein assaying for retroviral reverse transcriptase in the cell supernatant is presented as a method for identifying a virus that has infected a host cell (i.e., a virus capable of transferring its nucleic acid to a host cell); and at page 12, second paragraph, wherein methods for isolating a host cell colony are described as standard tissue cloning techniques, including cloning rings and clonal dilution.

Support for amendment to claim 16 is offered in Example 1, at pages 17-21, wherein retroviruses expressing a FeLV-A or FeLV-C Env variant on their surface are described as exemplary retroviruses for the practice of the present invention; at page 17, third paragraph, wherein Variable Region A (VRA) is described as an exemplary receptor-determining region

of feline leukemia viruses; in Figure 6 and description thereof at page 8, third paragraph, wherein a sequence comparison of the VRA receptor-determining domain of feline leukemia virus subgroup A and subgroup C is shown and amino acid substitutions are illustrated; in Example 2 at pages 21-22, wherein a method for infecting a host population with a virus comprising a random Env library is described; in Figure 7 and description thereof at page 8, fifth paragraph, and at page 17, second paragraph, wherein the Env expression vector used is shown and described, including the particular feature of this construct that the env gene is contained on the same packageable retroviral cassette as a drug selectable marker (i.e., a cell-selection marker); at page 2, first paragraph, wherein support that each member of the plurality of viruses comprises a nucleic acid that encodes an Env protein and a cell-selection marker is found; at page 11, eighth paragraph, wherein a definition for a "cell selection marker is presented; and at page 12, paragraphs 2 and 3, wherein a non-limiting list of cell selection markers is found and methods for detecting such cell selection markers are described. See also support cited with regard to claim 15.

Support for amendment to claims 19 and 26 is available in Example 2, at pages 21-22, wherein retroviruses expressing FeLV-A Env variants on their surface are described as exemplary retroviruses for the practice of the present invention. Support for amendment to claim 31 is presented in claim 31 as originally presented, and as described above for amendment to claim 15. Claim 17 has been cancelled thereby obviating rejection of this claim. No issue of new matter is introduced by these amendments.

Support for new claims 32-34 is found in the specification and the original claims. Specifically, new claims 32 and 33 are supported in originally filed claims 19 and 26. Support for new claim 34 is presented in claim 16, as presently amended. Support for amendments to claim 16 are presented herein above and are properly applied in the context of providing support for new claim 34. Support for new claim 35 is found in previously presented claim 31, for which support has been presented in applicants' Response dated May 29, 2003, and as described above for current amendments to claim 16. No issue of new matter is introduced by these claims.

Summary of the Invention

The present invention is directed to a method of identifying a retrovirus expressing a feline leukemia virus subgroup A (FeLV-A) or feline leukemia virus subgroup C (FeLV-C)

envelope (Env) variant on its surface, said retrovirus capable of transferring its nucleic acid to a host cell, the method comprising the steps of: (1) infecting a population of host cells with a random display library of retroviruses comprising a plurality of retroviruses, wherein each retrovirus differs in relation to other retroviruses of the plurality as to an amino acid sequence of a Variable Region A (VRA) of an exterior protein, wherein said exterior protein is a FeLV-A or FeLV-C Env protein and said plurality of retroviruses comprises retroviruses expressing a plurality of Env variants on their surface and (2) assaying for retroviral reverse transcriptase in cell supernatants of infected host cell populations, wherein detecting retroviral reverse transcriptase indicates a presence of a retrovirus expressing a FeLV-A or FeLV-C Env variant on its surface, the expression of which Env variant renders a retrovirus capable of infecting a host cell in the host cell population. Host cell colonies are isolated, thereby identifying a retrovirus expressing a FeLV-A or FeLV-C Env variant on its surface capable of transferring its nucleic acid to said host cells. Inasmuch as the invention is directed to identifying retroviruses which have a randomized sequence in their FeLV-A or FeLV-C Env protein that confers the ability to transfer viral nucleic acid to a host cell, the invention provides a screening method with which to identify a retrovirus expressing a FeLV-A or FeLV-C Env variant capable of infecting any mammalian cell.

Rejections 35 USC § 112

Claims 15-17, 19, 26, 31 have been rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors were in possession of the claimed invention at the time the application was filed. Claim 17 has been cancelled, thereby mooting the rejection of this claim. Claims 15 and 16, and dependent claims therefrom, and claim 31 have been amended to be directed to a retrovirus expressing a feline leukemia virus subgroup A (FeLV-A) or feline leukemia virus subgroup C (FeLV-C) Env variant on its surface. For reasons set out below, applicants request that this rejection be withdrawn.

The specification is fully descriptive of aspects of the invention pertaining to a retrovirus expressing a feline leukemia virus subgroup A (FeLV-A) Env variant on its surface. Moreover, applicants assert that the presentation of an alignment of the amino acid sequences comprising the VRA receptor-determining regions of FeLV-A and FeLV-C clearly

demonstrates that the teachings pertaining to FeLV-A are fully applicable to FeLV-C. See Figure 6 and description thereof. See also page 17, second paragraph, wherein the alignment the VRA regions is discussed in detail and an approach for introducing random amino acid substitutions into a FeLV VRA is set forth, and Figure 3, wherein an alignment of VRA regions is shown. An ordinarily skilled practitioner would appreciate from the specification, therefore, that the inventors were, at the time of filing, in possession of the claimed invention as it pertains to retroviruses expressing either a FeLV-A or FeLV-C Env variant on their surface. Moreover, a skilled practitioner would be aware that the Env proteins of FeLV-A and FeLV-C are structurally similar. Thus, applicants contend that the specification as filed presents clear evidence of the applicability of the methods of the invention to retroviruses expressing either a FeLV-A or FeLV-C Env variant on their surface. Accordingly, applicants submit that the rejection of claims 15-16, 19, 26, 31, as presently amended, is improper and respectfully request that this rejection be withdrawn.

In view of the comments at page 5 of the Office Action pertaining to the Examiner's interpretation of a passage in the specification, applicants have deemed it necessary to clarify the meaning of the passage as written. While it is true that FeLV-A Env protein was used in the methods of the present invention, in part, because its Env receptor binding domain has a relatively simple structure which has been well characterized and consists of a short stretch of amino acids, it **cannot** be properly extrapolated that this is the only FeLV Env protein for which such determinations have been made. Indeed, FeLV-C Env protein is known to be structurally similar to FeLV-A Env protein and exhibits all of the above characteristics. The Examiner's interpretation is, therefore, inconsistent with the available experimental data and contradictory to prevailing scientific opinion.

In contrast to the Examiner's contention that the selectable markers described in the specification are allegedly adapted for FeLV retroviruses, applicants assert that the cell selection markers of the present invention are widely used for a diverse array of applications. Support for applicants' assertion is provided in a number of standard manuals of molecular biology known to an ordinarily skilled artisan and available in essentially any institute wherein molecular biological techniques are practiced. Such manuals include, for example, Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York; and Ausubel et al., 1988, Current Protocols in Molecular Biology,

John Wiley & Sons, New York. In view of the above, applicants assert that the Examiner's position with regard to the cell selection markers described in the specification and any perceived limitation as to their applicability to only FeLV is completely without basis in available scientific literature. Moreover, the cell selection markers described in the specification are used in the context of retroviral expression cassettes or retroviruses comprising a library of FeLV-A Env variants. Applicants respectfully assert that the cell selection markers are **not** described in the specification in the context of FeLV, which further erodes the Examiner's position in this regard.

For the record, however, the specification presents ample guidance relating to using cell selection markers and means for selecting cells expressing these markers. See page 11, bridging paragraph to page 12, third paragraph for a non-limiting list of different cell selection markers and methods that may be used for identifying (drug selection, enzymatic markers, antibodies, fluorescence tagged molecules) and isolating (cell-sorting, cloning rings, clonal dilution, hapten-coated magnetic beads) cells into which an infective retroviral nucleic acid molecule has been incorporated on a genomic level. These techniques are not viewed by skilled practitioners as specifically adapted for use in the context of retroviruses or FeLV. Moreover, as stated above, such techniques directed to the expression of cell-selection markers and selection of cells within a population that express such markers are well known and regularly practiced by skilled artisans. With regard to retroviruses, genes encoding these markers can be packaged into a retrovirus by virtue of their covalent attachment to (i.e., colinearity with) a retroviral genome that comprises a "packaging signal" and other elements of the retroviral replication machinery. This packaging signal allows the gene for any selectable marker to be packaged into a retroviral particle; after several processing steps by the retroviral machinery during the infection cycle, such selectable markers are incorporated into a target cell genome (i.e., an infected cell) where they are expressed.

In one aspect of the invention, for example, a specifically targeted virus of the invention is identified by virtue of the expression of a gene encoding a cell selection marker, which is colinear with the mutated envelope gene. As shown in the specification, the pRVL vector of Example 1 comprises a G418 resistance marker which is used to select for resistant cells. Drug resistant cell clones are isolatable in accordance with the methods set forth in the

present specification and by other techniques commonly used in molecular biology laboratories and well known to those skilled in the art. Techniques for separating one colony of drug resistant cells from another colony of drug-resistant cells using cloning rings or by clonal dilution, for example, are common and widely practiced molecular biology techniques. Other cell selection markers and methods for isolation/separation of singly infected cells are described and referenced in the specification. See, for example, page 12, second paragraph. Indeed, any of the selectable markers listed therein may be substituted for the G418 resistance gene used in Examples 1 and 2. In summary, isolation of virally infected cells can be achieved using these cell selection markers and methods directed to distinguishing infected cells, which express an incorporated selectable marker, from uninfected cells provide the means to identify a virally infected cell.

The Examiner appears to maintain that a 50% probability of obtaining a stop codon during randomization of a receptor binding domain renders the success of the present invention reliant on a specific FeLV Env protein. Applicants respectfully disagree with the Examiner's position. Inasmuch as the amended claims are, however, directed to retroviruses expressing a variant of either a FeLV-A Env protein or the **structurally similar** FeLV-C Env protein, applicants believe that the amendments to the claims are curative of any rejection based on the Examiner's above recited position. See also arguments set forth herein above that pertain to the similarities of FeLV-A and FeLV-C Env proteins and support thereto identified in the specification.

The Examiner repeatedly refers to amended claim 5, step 2 on page 7 of the Office Action, but applicant assumes that the Examiner is actually referring to amended claim 15, step 2. The Examiner maintains that the passages identified in the specification as supportive of step 2 are insufficient. Applicants respectfully disagree. To more clearly set forth the methods steps of the claim, however, and remove any perceived repetitiveness, claim 15 has been amended. Accordingly, applicants believe that the amendments to claim 15 have obviated the rejection of this claim and respectfully request that the rejection be withdrawn.

Claims 15-16, and dependent claims therefrom, and claim 31 have been amended to be directed to a method of identifying a retrovirus expressing either a FeLV-A or FeLV-C Env variant on its surface, which retrovirus is capable of transferring its nucleic acid to a host cell, wherein a population of host cells is infected with a random display library of

retroviruses comprising a plurality of retroviruses, wherein each retrovirus differs in relation to other retroviruses of the plurality as to an amino acid sequence of a Variable Region A (VRA) of an Env protein or wherein each retrovirus differs in relation to other retroviruses of the plurality as to an amino acid sequence of an exterior protein, i.e., an Env protein comprising random amino acid sequences in the VRA. The claims, as amended, are therefore believed to be directed to subject matter for which the specification presents ample written description and guidance and, therefore, clearly demonstrates that the inventors were in possession of the claimed invention at the time of filing.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 15-16, 19, 26, 31 under 35 U.S.C. §112, first paragraph.

Certain additional issues raised by the Examiner are believed by applicants to require specific response so that the record is clarified and applicants' position is understood. At page 4 of the Office Action, for example, the Examiner states that a passage in the specification (at page 19, penultimate paragraph) supports the Examiner's position that "there is nothing in the specification or prior art teachings that indicates the extrapolation or applicability of the specific retrovirus, Felv to any other retroviruses. The passage is quoted as follows: "although the C subgroup FelV has a broad range, EF shows very highly specific infection of the D17 canine osteosarcoma cells". Applicants assert that EF was selected for the feature of altered infectivity, that is, the ability to infect D17 canine osteosarcoma cells. The generation of a virus particle having altered cellular specificity is proof that the methods of the present invention are effective for their intended purpose. The passage cited by the Examiner has no relevance to the alleged lack of extrapolation or applicability of the specific virus to other retroviruses.

Another statement, which is found at page 5 of the Office Action, also necessitates rebuttal on the part of applicants. Examiner suggests that a passage from Battini et al. (PNAS) supports the Examiner's position "that the requirement or condition of a specific retrovirus as Felv A is different from even those of its own Felv family, let alone, for any or all types of different retroviruses". The passage apparently appears at page 1385, and is quoted as follows: "although present in many copies in mouse genome, ..murine leukemia viruses cannot infect cells from laboratory mice because of the lack of a functional cell surface receptor required for virus entry". Applicants submit that the above passage is not

germane to the present invention. While it is understood that murine leukemia viruses cannot infect cells from laboratory mice that lack a functional cell surface receptor for the virus, which is required for virus entry, it is not apparent how this information can be properly applied to the characteristics of **FeLV-A**. Applicants, therefore, dispute the relevance of the passage to **FeLV-A** or the method of the invention.

Claims 15-17, 19, 26, and 31 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Claim 17 has been cancelled, thus rendering moot the rejection of this claim. Claims 15-16 and 31 have been amended in accordance with the Examiner's suggestions to more clearly indicate method steps involved in the practice of the invention. Claim 16 has been amended to clarify that a virus of the invention comprises nucleic acid sequences encoding a Env variant and a cell-selection marker. The base claim from which claim 26 depends has been amended to render apparent how a virus of the invention is identified. Accordingly, applicants believe that the amendments to claims 15-16 and 31, and dependent claims therefrom, have obviated the rejection of these claims under 35 U.S.C. §112, second paragraph.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw the rejection of the instant claims under 35 U.S.C. §112.

Rejections Under 35 U.S.C. § 102 and § 103

The Examiner has rejected claims 15-17, 19, 26, and 31 under 35 U.S.C. 102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. 103 (a) as obvious over Buchholz et al. (Nature Biotechnology). Claim 17 has been cancelled, thereby obviating these rejections of the claim.

Applicants respectfully submit that the disclosure of Buchholz et al. fails to anticipate claims 15-16, 19, 26, and 31, as amended, of the present invention. Specifically, Buchholz et al. do not teach or suggest the method of the present invention wherein random peptides are incorporated into a **VRA** of **either a FeLV-A or FeLV-C** Env protein of a retroviral library wherein retroviruses express **either the FeLV-A or FeLV-C Env variant on their surface**. In the absence of such teaching, this reference fails to anticipate the method of the instant invention. Accordingly, applicants assert that the rejection of claims 15-16, 19, 26, and 31, as

amended, under 35 U.S.C. 102(b) as allegedly anticipated by Buchholz et al. is improper and respectfully request, therefore, that the rejection be withdrawn.

Applicants also purport that Buchholz et al. fail to render obvious presently amended claims 15-16, 19, 26, and 31. As described herein above, this reference fails to provide guidance with regard to the incorporation of random peptides into a **VRA** region of a receptor binding domain of **either a FeLV-A or FeLV-C** Env protein of a retroviral library wherein retroviruses express **either the FeLV-A or FeLV-C Env variant on their surface**. Moreover, the reference is also defective relating to teachings that such an approach could be used for the purpose of identifying a **retrovirus having altered host cell specificity**. The Buchholz et al. reference describes the construction of plasmids encoding replication-competent **murine leukemia viruses** displaying a virally encoded epidermal growth factor (EGF) domain at the **N-terminus** of the envelope glycoprotein. Notably, the Bucholz et al. reference is directed to the generation of a random library that was used to introduce **a protease cleavage site,** not a receptor targeting region, into the N-terminus of the envelope glycoprotein. In contrast, the present invention is directed to the incorporation of random peptides into a **VRA** region of a receptor binding domain (cell targeting region) of an **FeLV** Env protein; this region is located approximately 50 amino acid residues **downstream** of the N-terminus. The incorporation of random sequences into the **VRA** interrupts the amino acid sequence of the native Env protein and, depending on the insertion sequence, alters the functional activity of the Env protein to change infective properties of the mutated Env protein. Inasmuch Buchholz et al. fail to suggest a method wherein random peptide sequences are incorporated into the particular receptor binding domain of the Env protein which is targeted in the present invention (i.e., the VRA region), this reference lacks the teaching to render obvious the method of the present invention. Moreover, as argued extensively by the Examiner, that which is applicable to one retrovirus is not necessarily applicable to another. The Buchholz et al. reference is directed to an analysis of variations in the N-terminus of the murine leukemia virus Env protein. As such, the findings of Buchholz et al. are not properly extrapolated to render obvious properties of other Env proteins, such as those of FeLV-A and FeLV-C. Applicants, therefore, submit that the rejection of presently amended claims 15-16, 19, 26, and 31 under 35 U.S.C. 103 (a) as obvious over Buchholz et al. (Nature Biotechnology) is inappropriate and respectfully request that the rejection be

withdrawn.

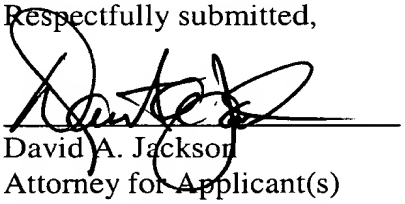
Fees

No fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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Attachments: Petition for One-Month Extension of Time
Request for Continued Examination